



Population Pharmacokinetics of High-Dose Continuous-Infusion Meropenem and Considerations for Use in the Treatment of Infections Due to KPC-Producing *Klebsiella pneumoniae*

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ABSTRACT We assessed the population pharmacokinetics of high-dose continuous-infusion (HDCI) meropenem in a cohort of patients with *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae* (KPC-Kp) infections. Monte Carlo simulations were used to define the permissible HDCI meropenem regimens that could be safely considered for the treatment of KPC-Kp infections due to meropenem-resistant strains. Permissible doses were arbitrarily defined as those associated with a $\leq 10\%$ to 15% likelihood of meropenem steady-state concentrations (C_{ss}) of >100 mg/liter. Probabilities of target attainment (PTA) of four incremental pharmacodynamic determinants for meropenem efficacy ($100\% T_{>1 \times MIC}$, $100\% T_{>2 \times MIC}$, $100\% T_{>3 \times MIC}$, and $100\% T_{>4 \times MIC}$, where “ $T_{>MIC}$ ” represents the time during which the plasma concentration of this time-dependent antibacterial agent is maintained above the MIC for the pathogen) in relation to different classes of renal function were calculated. The cumulative fractions of response (CFR) for the permissible HDCI meropenem regimens were calculated against the MIC distribution of the KPC-Kp clinical isolates that were collected routinely at our University Hospital between 2013 and 2016 ($n = 169$). Ninety-seven meropenem C_{ss} were included in the analysis. The final model included creatinine clearance (CrCL) as a covariate and explained 94% of the population variability. Monte Carlo simulations based on licensed dosages of up to 6 g/day predicted an acceptable PTA ($>80\%$) of $100\% T_{>1 \times MIC}$ against KPC-Kp with a meropenem MIC of ≤ 32 mg/liter in patients with a CrCL level of <130 ml/min. Dosages of 8 g/day were needed for achieving the same target in patients with CrCL at levels of 130 to 200 ml/min. In dealing with pathogens with a meropenem MIC of 64 mg/liter, HDCI regimens using meropenem at higher than licensed levels should be considered. In these cases, real-time therapeutic drug monitoring could be a useful adjunct for optimized care. The predicted CFR were $>75\%$ in all of the classes of renal function.

KEYWORDS meropenem, continuous infusion, PK/PD, KPC-producing *Klebsiella pneumoniae*, *K. pneumoniae*, KPC+

Carbapenem-resistant *Enterobacteriaceae* (CRE) have spread globally among Gram-negative bacteria. The presence of nationwide CRE endemicity caused several infection outbreaks in many countries, including Italy (1, 2). Among the CRE outbreaks, those due to *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae* (KPC-Kp) are burdened by high mortality rates (3, 4).

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Unfortunately, optimal antimicrobial treatment of KPC-Kp infections has not yet been defined. Recent data suggested that antimicrobial combination therapy may be superior to monotherapy (3–6) and that the inclusion of meropenem as the backbone in the combination regimens should be pursued to as great a degree as possible, whenever feasible (7–9).

It has recently been suggested that pharmacokinetic/pharmacodynamic (PK/PD) optimization of antimicrobials with activity against Gram-negative bacteria may represent the way forward for overcoming the *in vitro* theoretical resistance associated with multidrug-resistant (MDR) Gram-negative bacteria (10).

Consistently, extended infusion (EI) of meropenem or continuous infusion (CI) of meropenem or both are being increasingly recommended for optimal use under these circumstances (7, 10, 11). The intent is that of maximizing the time during which the plasma concentration of this time-dependent antibacterial agent is maintained above the MIC for the pathogen ($T_{>MIC}$).

The use of EI meropenem has been recommended in the treatment of KpC-Kp infections in the presence of clinical isolates with a meropenem MIC of up to 8 mg/liter (7, 8). Data from Tumbarello et al. (4) and Daikos et al. (9) support the supposition that an EI of meropenem at 6 g/day may work in these cases, with a higher mortality rate when MICs are higher. The possibility that this approach might be feasible even against KpC-Kp infections due to strains with higher meropenem MICs is still to be demonstrated (12, 13). In this regard, we recently showed that high-dose CI (HDCl) meropenem, in combination with other antimicrobials with activity against Gram-negative bacteria, was effective in the treatment of KPC-Kp infections (mainly of the bloodstream) due to strains with a meropenem MIC of up to 64 mg/liter (14).

The aim of this study was to assess the population pharmacokinetics of HDCl meropenem in a cohort of patients with KPC-Kp infections, with the intent of defining permissible dosing regimens that could be safely considered for the treatment of KPC-Kp infections due to meropenem-resistant strains.

RESULTS

Study population. Data from 30 adult patients with KPC-Kp infections who were enrolled in a previously published retrospective study (14) were included for the population pharmacokinetic analysis in this study. Median (range) age, weight, and creatinine clearance (CrCL) level were 62.5 years (34.0 to 87.0 years), 69.5 kg (46.0 to 100.0 kg), and 80.0 ml/min (23.1 to 200.0 ml/min), respectively. The majority of the patients had bloodstream infections (60%) and received therapeutic drug monitoring (TDM)-guided HDCl meropenem regimens ranging between 500 mg every 8 h over 8 h and 3,500 mg every 6 h over 6 h.

Population pharmacokinetic model. Overall, 97 meropenem C_{ss} values were included in the population pharmacokinetic analysis (median value, 43.42 mg/liter; interquartile range [IQR], 28.91 to 82.03 mg/liter). The 2-compartment model performed better overall than the 1-compartment model (objective function value [OFV], 829.2 versus 858.6; Akaike criterion value, 839.8 versus 864.8; R^2 of the observed versus individual predicted concentration, 0.936 versus 0.862) and was preferred as the base structural model. CrCL was the only covariate that improved the model fit. After inclusion in the model of CrCL as a covariate with CL and k_{pc} , OFV improved (from 829.2 to 805.9).

The final model was as follows:

$$CL = 2.42 + 0.025 \times CrCL$$

$$k_{pc} = 2.624 - 0.005 \times CrCL$$

where CL, k_{pc} , and CrCL represent the values of meropenem CL, of meropenem first-order rate constant for transfer from the peripheral to the central compartment, and of CrCL estimated by means of the Cockcroft-Gault formula, respectively.

Figure 1 shows the diagnostic plot for the final covariate model. The correlation between the observed and the population-predicted meropenem concentrations for

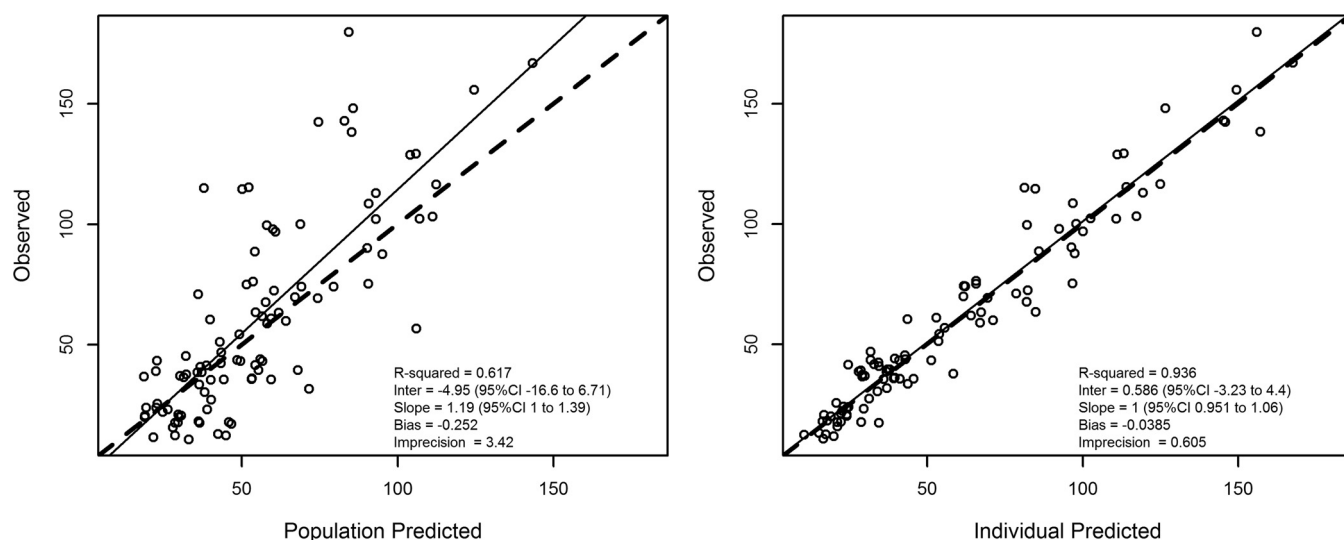


FIG 1 Diagnostic plot for the final population pharmacokinetic model. Observed versus population-predicted plasma concentrations are shown in the left panel, whereas observed versus individual predicted plasma concentrations are shown in the right panel.

the population estimate was good ($r^2 = 0.617$), and the correlation improved after maximum *a posteriori* (MAP) Bayesian estimation ($r^2 = 0.936$), with acceptable bias and precision (-0.0385 mg/liter and 0.605 mg/liter, respectively). The visual predictive check (VPC) plot of the final model is depicted in Fig. 2.

Mean (\pm standard deviation [SD]) and median (coefficient of variation [CV]) estimates of the pharmacokinetic parameters in the final model are summarized in Table 1.

Monte Carlo simulation for estimation of permissible HDCl meropenem regimens predicting optimal target drug exposure in patients with KPC-Kp infection and various degrees of renal function. Simulated levels of meropenem C_{ss} achievable with the various HDCl meropenem regimens in relation to four different classes of renal

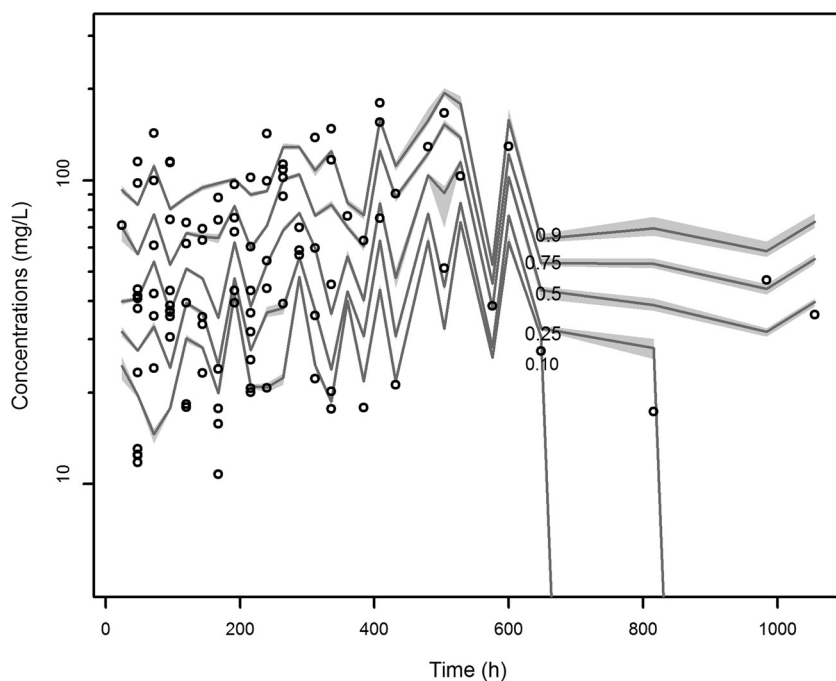


FIG 2 Visual predictive check plot of meropenem plasma concentrations versus time for the final covariate model. Gray shadings display predicted intervals of simulated data.

TABLE 1 Parameter estimates for the final population pharmacokinetic model of HDCl meropenem in patients with KPC-producing *Klebsiella pneumoniae* infections^a

Unit	Value			
	CL (liters/h)	V _c (liters)	k _{cp} (h ⁻¹)	k _{pc} (h ⁻¹)
Mean	4.43	28.15	6.93	2.11
SD	2.31	9.52	2.62	0.97
Coefficient of variation (%)	52.22	33.82	37.83	46.17
Median	3.87	32.43	7.77	2.48

^aCL, total body clearance; HDCl, high-dose continuous infusion; k_{cp}, first-order intercompartmental rate constant of transfer from the central compartment to the peripheral compartment; k_{pc}, first-order intercompartmental rate constant of transfer from the peripheral compartment to the central compartment; V_c, volume of the central compartment.

function are depicted in Fig. 3. Maximum permissible HDCl meropenem regimens (defined as those leading to a <10% to 15% probability of minimum concentration [C_{min}] levels of >100 mg/liter) were identified as follows: 2,000 mg every 8 h over 8 h (regimen G) for CrCL of 10 to 39 ml/min, 2,000 mg every 6 h over 6 h (regimen I) for CrCL of 40 to 79 ml/min, 3,000 mg every 8 h Cl (regimen K) for CrCL of 80 to 129 ml/min, and 2,750 mg every 6 h Cl (regimen M) for CrCL of 130 to 200 ml/min.

PTA and CFR achievable with the permissible HDCl meropenem regimens. In regard to the minimum PK/PD target of 100% T_{>1×MIC}, the permissible HDCl meropenem regimens predicted acceptable (>80%) PTAs against KPC-Kp with a meropenem MIC of up to 32 mg/liter in all of the classes of renal function (Table 2). Conversely, only suboptimal PTAs, ranging between 52.2% and 64.7%, were predicted against KPC-Kp with a meropenem MIC of 64 mg/liter.

In considering more-aggressive PK/PD targets (100% T_{>2×MIC}, 100% T_{>3×MIC}, and 100% T_{>4×MIC}), the permissible HDCl meropenem regimens predicted acceptable PTAs against KPC-Kp strains with a meropenem MIC of up to 16 mg/liter (MIC thresholds of 16 mg/liter for 100% T_{>2×MIC} in all of the classes of renal function; 16 mg/liter for 100% T_{>3×MIC} in all of the classes of renal function, except CrCL [130 to 200 ml/min]; and 8 mg/liter for 100% T_{>4×MIC} in all of the classes of renal function).

Figure 4 shows the distributions of the PTAs of the minimum PK/PD target of 100% T_{>1×MIC} achievable with some permissible HDCl meropenem regimens in relation to the distribution of drug MICs of 169 KPC-Kp clinical isolates that were collected at our University Hospital during the period 2013 to 2016. The majority (69.2%) of these KPC-Kp clinical isolates had a meropenem MIC of ≤32 mg/liter; 20.1% had a meropenem MIC of 64 mg/liter; and only 10.7% had a meropenem MIC of >64 mg/liter.

The CFRs for the minimum PK/PD target of 100% T_{>1×MIC} against these KPC-Kp clinical isolates are summarized in Table 3. The CFRs for the highest permissible HDCl meropenem regimens were >75% in all classes of renal function.

Figure 5 depicts a dosing algorithm for choosing the most advisable HDCl meropenem regimen in relation to different classes of renal function, which may be considered for the empirical treatment of suspected KPC-Kp infections. The approach is feasible in clinical settings similar to ours, which is characterized by KPC-Kp clinical isolates with a high (≥70%) frequency of meropenem MICs of ≤32 mg/liter and a low (≤10%) frequency of meropenem MICs of >64 mg/liter.

DISCUSSION

In this study, we assessed the population pharmacokinetics of meropenem in patients receiving HDCl for the treatment of KPC-Kp infections. Subsequently, we sought to identify permissible HDCl meropenem regimens which may be considered for optimal treatment of KPC-Kp infections due to meropenem-resistant strains in patients with different classes of renal function.

Although the population pharmacokinetics of meropenem was investigated in various patient populations (15–19), this is the first time that it was assessed during HDCl. The final model accounted for up to 94% of the variability in meropenem concentrations and adequately fitted the drug concentration-time data.

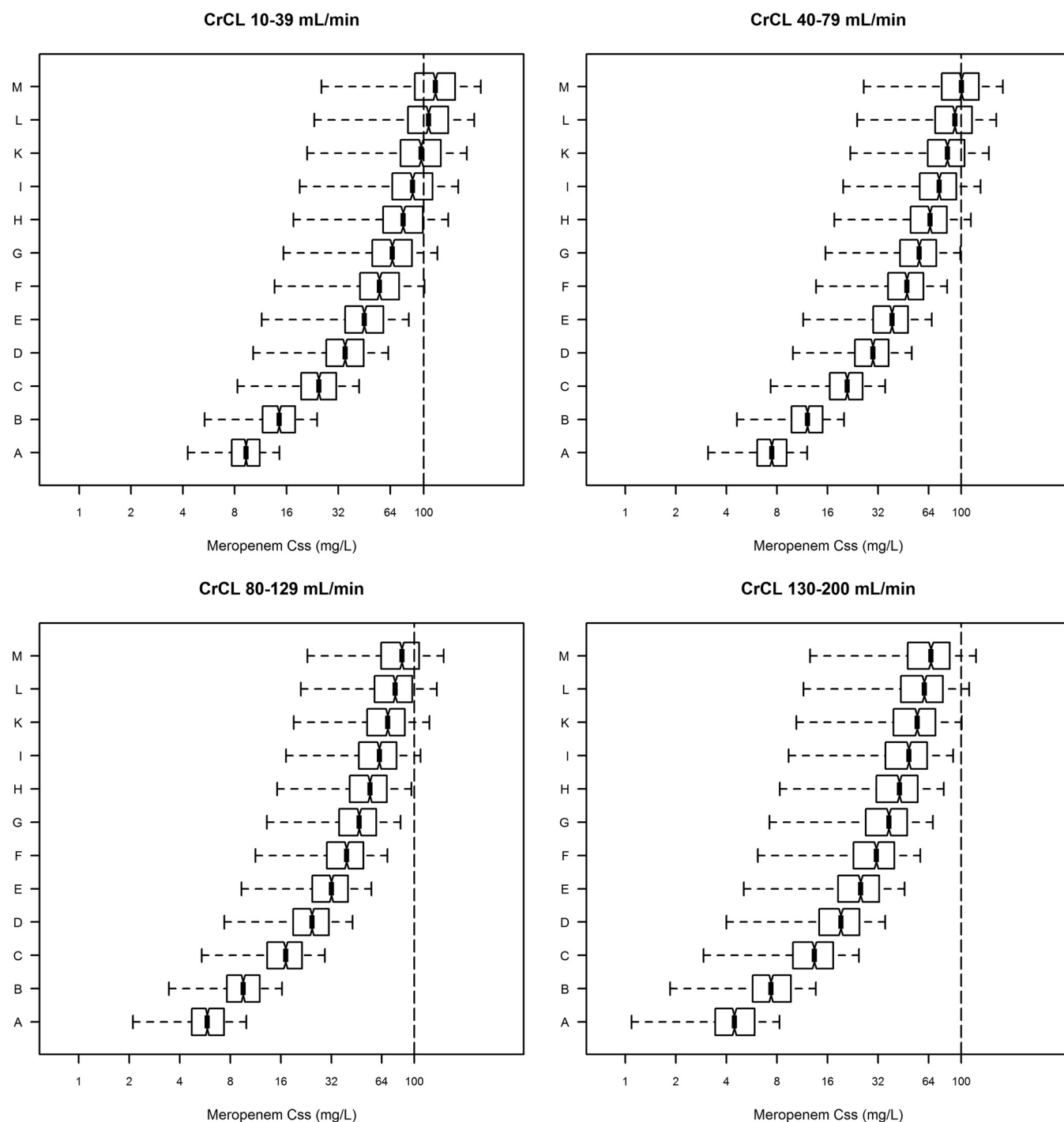


FIG 3 Box (median, 25th and 75th percentile) and whiskers (5th and 95th percentile) plots of simulated steady-state plasma concentrations (C_{ss}) achievable with escalating high-dose continuous-infusion meropenem regimens (A, 125 mg every 6 h over 6 h; B, 250 mg every 6 h over 6 h; C, 500 mg every 6 h over 6 h; D, 1,000 mg every 8 h over 8 h; E, 1,000 mg every 6 h over 6 h; F, 1,250 mg every 6 h over 6 h; G, 2,000 mg every 8 h over 8 h; H, 1,750 mg every 6 h over 6 h; I, 2,000 mg every 6 h over 6 h; K, 3,000 mg every 8 h over 8 h; L, 2,500 mg every 6 h over 6 h; M, 2,750 mg every 6 h over 6 h) in relation to different classes of renal function. Vertical dashed lines identify the safety threshold.

Our findings are in line with those observed in other patient populations (16, 20–22). Population pharmacokinetics of meropenem during CI was previously assessed only once, among postsurgical patients receiving the fixed dose of 3 g/day (22). The median plasma meropenem C_{ss} was 13.2 mg/liter, and meropenem CL was well correlated with all of the estimates of renal function. Our results are in agreement with these findings

TABLE 2 Permissible HDCl meropenem regimens enabling acceptable PTA of the PK/PD targets in relation to different classes of renal function and to the meropenem MIC of the invading KPC-producing *Klebsiella pneumoniae* strain^a

Class of renal function (ml/min)	PK/PD target	Regimen at meropenem MIC (mg/liter) of:						
		1	2	4	8	16	32	64
10–39	100% $T_{>1 \times \text{MIC}}$	125 mg q6h CI	125 mg q6h CI	125 mg q6h CI	250 mg q6h CI	500 mg q6h CI	1,000 mg q6h CI	2,000 mg q8h CI*
	100% $T_{>2 \times \text{MIC}}$	125 mg q6h CI	125 mg q6h CI	250 mg q6h CI	500 mg q6h CI	1,000 mg q6h CI	2,000 mg q8h CI*	
	100% $T_{>3 \times \text{MIC}}$	125 mg q6h CI	125 mg q6h CI	500 mg q6h CI	1,000 mg q8h CI	2,000 mg q8h CI		
	100% $T_{>4 \times \text{MIC}}$	125 mg q6h CI	250 mg q6h CI	500 mg q6h CI	1,000 mg q6h CI	2,000 mg q8h CI*		
40–79	100% $T_{>1 \times \text{MIC}}$	125 mg q6h CI	125 mg q6h CI	125 mg q6h CI	250 mg q6h CI	1,000 mg q8h CI	1,250 mg q6h CI	2,000 mg q6h CI*
	100% $T_{>2 \times \text{MIC}}$	125 mg q6h CI	125 mg q6h CI	250 mg q6h CI	1,000 mg q8h CI	1,250 mg q6h CI	2,000 mg q6h CI*	
	100% $T_{>3 \times \text{MIC}}$	125 mg q6h CI	250 mg q6h CI	500 mg q6h CI	1,000 mg q6h CI	2,000 mg q6h CI		
	100% $T_{>4 \times \text{MIC}}$	125 mg q6h CI	250 mg q6h CI	1,000 mg q8h CI	1,250 mg q6h CI	2,000 mg q6h CI*		
80–129	100% $T_{>1 \times \text{MIC}}$	125 mg q6h CI	125 mg q6h CI	125 mg q6h CI	500 mg q6h CI	1,000 mg q8h CI	2,000 mg q8h CI	3,000 mg q8h CI*
	100% $T_{>2 \times \text{MIC}}$	125 mg q6h CI	125 mg q6h CI	500 mg q6h CI	1,000 mg q8h CI	2,000 mg q8h CI	3,000 mg q8h CI*	
	100% $T_{>3 \times \text{MIC}}$	125 mg q6h CI	250 mg q6h CI	500 mg q6h CI	1,250 mg q6h CI	3,000 mg q8h CI		
	100% $T_{>4 \times \text{MIC}}$	125 mg q6h CI	500 mg q6h CI	1,000 mg q8h CI	2,000 mg q8h CI	3,000 mg q8h CI*		
130–200	100% $T_{>1 \times \text{MIC}}$	125 mg q6h CI	125 mg q6h CI	250 mg q6h CI	500 mg q6h CI	1,000 mg q6h CI	2,000 mg q6h CI	2,750 mg q6h CI*
	100% $T_{>2 \times \text{MIC}}$	125 mg q6h CI	250 mg q6h CI	500 mg q6h CI	1,000 mg q6h CI	2,000 mg q6h CI	2,750 mg q6h CI*	
	100% $T_{>3 \times \text{MIC}}$	125 mg q6h CI	500 mg q6h CI	1,000 mg q8h CI	2,000 mg q8h CI	2,750 mg q6h CI*		
	100% $T_{>4 \times \text{MIC}}$	250 mg q6h CI	500 mg q6h CI	1,250 mg q6h CI	2,000 mg q6h CI	2,750 mg q6h CI*		

^aAcceptable PTA, $>80\%$; HDCl, high-dose continuous infusion. The HDCl meropenem regimens highlighted with gray shading and asterisks were associated with suboptimal PTAs. Continuous infusion should be provided through reconstitution of the solution every 6 to 8 h at the maximum.

and suggest that the meropenem C_{ss} may be much higher during HDCl (median value, 43.42 mg/liter).

Several authors advocated the use of EI meropenem for the treatment of infections caused by KPC-Kp with a meropenem MIC of ≤ 8 mg/liter (4, 6–9, 12). We recently showed that maintenance of 100% $T_{>1 \times \text{MIC}}$ with HDCl meropenem may represent a valuable tool in improving clinical outcome even in dealing with infections caused by KPC-Kp with a meropenem MIC of ≤ 64 mg/liter (14). In that study, dosages of meropenem higher than those licensed were used on several occasions (14).

The use of doses of meropenem higher than those licensed is increasingly being advocated for the treatment of life-threatening infections due to MDR pathogens (23–25). This may cause some concerns about the toxicity risk. Early experiences with these types of doses have been encouraging; however, much more data are needed concerning the safety of these exposures. In our study, no drug-related adverse events occurred, even in the presence of C_{ss} of up to 143 mg/liter (14). Conversely, a very recent retrospective study revealed the potential existence of concentration-toxicity relationships for adverse effects of meropenem during high-dose intermittent infusion (1 to 6 g/day at 8-to-12-h intervals) (26). Meropenem C_{min} values of >64.2 mg/liter were associated with a 50% probability of developing a neurotoxicity event. However, the authors recognized that the retrospective design and the potential confounding effect of comedications hindered the ability to establish the causation of toxicity as directly attributable to meropenem therapy. Additionally, it should not be overlooked that the threshold value referred to the C_{min} during intermittent infusion, and this means that the peak concentrations should have been much higher, probably far above 100 mg/liter. This seems to suggest that adoption of the value of 100 mg/liter as the safety threshold for meropenem C_{ss} during HDCl could be sufficiently safe. Consistently, this dosing approach is limited to continuous infusions and would not be applicable to giving these same doses by other infusion strategies (including EI and intermittent-infusion strategies).

In the retrospective study of HDCl meropenem among patients with KPC-Kp infections, successful clinical outcome was significantly associated with 100% $T_{>1 \times \text{MIC}}$ (odds ratio [OR] = 10.556; 95% confidence interval [CI], 1.612 to 69.122; $P = 0.014$) and with 100% $T_{>4 \times \text{MIC}}$ (OR = 12.250; 95% CI, 1.268 to 118.361; $P = 0.030$) (14). Interestingly, favorable clinical response was obtained in more than 60% (8/13) of patients who were infected by meropenem-resistant KPC-Kp strains with a meropenem MIC ranging between 16 and 64 mg/liter.

In this study, Monte Carlo simulations performed with permissible HDCl meropenem

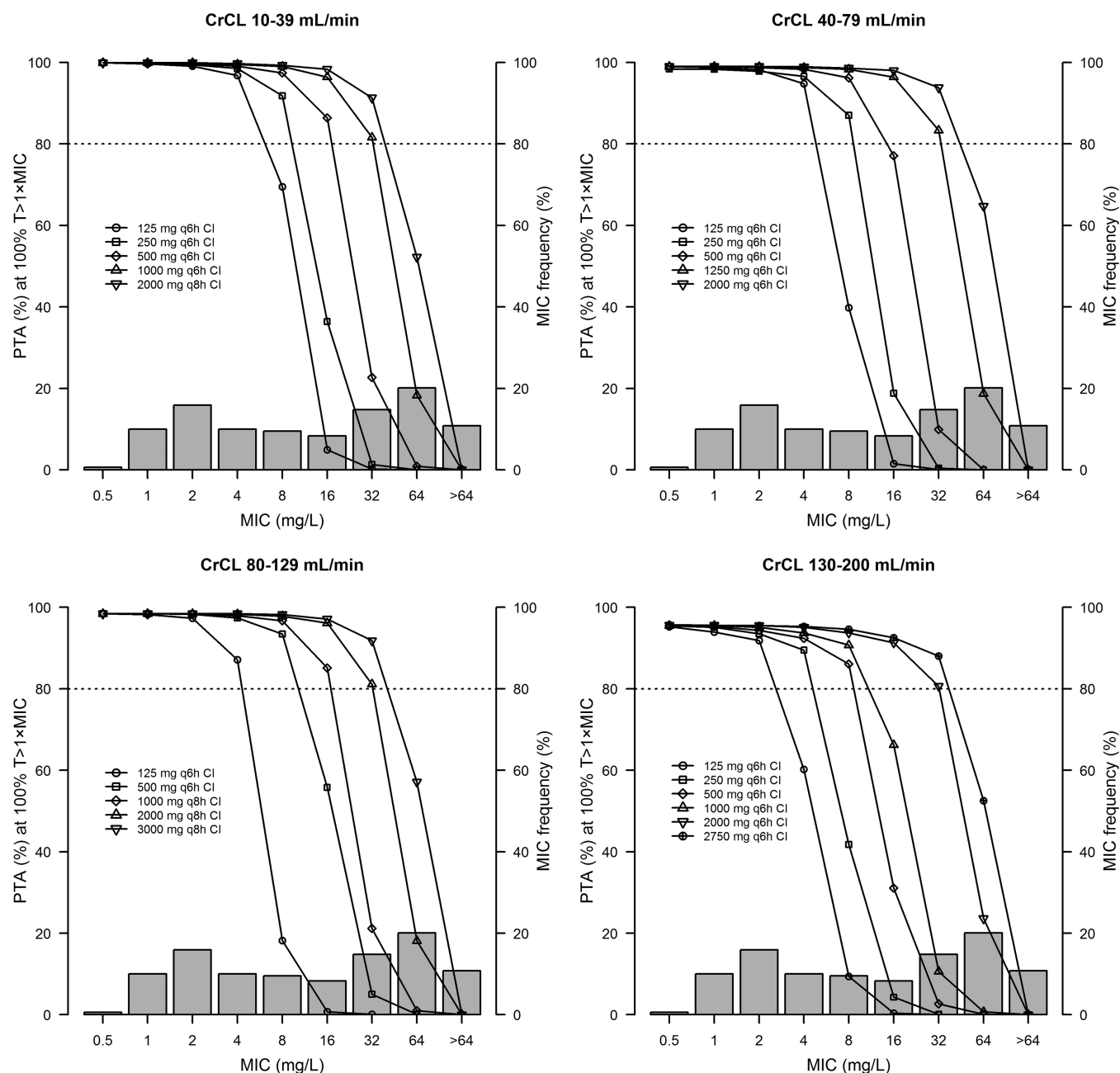


FIG 4 Probability of target attainment (PTA) of 100% $T > 1 \times \text{MIC}$ with some permissible high-dose continuous-infusion meropenem regimens in relation to different classes of renal function. Gray boxes identify the MIC distribution frequencies of 169 *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae* isolates collected at our hospital in the period 2013 to 2016. Horizontal dotted lines identify the threshold for acceptable PTA (80%).

regimens based on licensed dosages of up to 6 g/day predicted acceptable and/or desired PTAs of 100% $T > 1 \times \text{MIC}$ in the majority of patients having infections caused by KPC-Kp with a meropenem of $\text{MIC} \leq 32$ mg/liter. The only exception is that of patients with augmented renal clearance ($\text{CrCL} \geq 130$ ml/min), for whom the HD CI meropenem regimen should be of 8 g/day.

In dealing with infections caused by KPC-Kp with a meropenem MIC of 64 mg/liter, HD CI regimens with meropenem dosages higher than those licensed should always be considered. However, even with the maximum permissible HD CI meropenem regimens, the PTAs of 100% $T > 1 \times \text{MIC}$ were always suboptimal, ranging between 50% and 65%. Consistently, the use of real-time TDM-guided HD CI meropenem could be a useful adjunct for optimized care in those cases.

TABLE 3 CFR of the permissible HDCl meropenem regimens for the minimum PK/PD target of 100% $T_{>1 \times \text{MIC}}$ against the meropenem MIC distribution of 169 KPC-Kp clinical isolates collected at our hospital in the period 2013 to 2016^a

Class of renal function (ml/min)	Meropenem daily dose (mg)	CFR (%)
10–39	125 mg q6h CI	43.19
	250 mg q6h CI	48.32
	500 mg q6h CI	56.44
	1,000 mg q6h CI	69.79
	2,000 mg q8h CI	78.64
40–79	125 mg q6h CI	39.64
	250 mg q6h CI	45.66
	500 mg q6h CI	53.20
	1,250 mg q6h CI	69.72
	2,000 mg q6h CI	81.43
80–129	125 mg q6h CI	36.56
	500 mg q6h CI	50.21
	1,000 mg q8h CI	55.58
	2,000 mg q8h CI	69.05
	3,000 mg q8h CI	79.17
130–200	125 mg q6h CI	31.65
	250 mg q6h CI	38.40
	500 mg q6h CI	45.66
	1,000 mg q6h CI	54.63
	2,000 mg q6h CI	68.29
	2,750 mg q6h CI	75.93

^aCFR, cumulative fraction of response; HDCl, high-dose continuous infusion; KPC-Kp, *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae*. Continuous infusion should be provided through reconstitution of the solution every 6 to 8 h at the maximum.

It is worth noting that in dealing with KPC-Kp clinical isolates with a meropenem MIC of ≤ 16 mg/liter, the strategy based on permissible HDCl regimens may allow the achievement of more-aggressive PK/PD targets for meropenem (up to 100% $T_{>4 \times \text{MIC}}$). This could be helpful, considering that maintenance of 100% $T_{>5 \times \text{MIC}}$ was the most

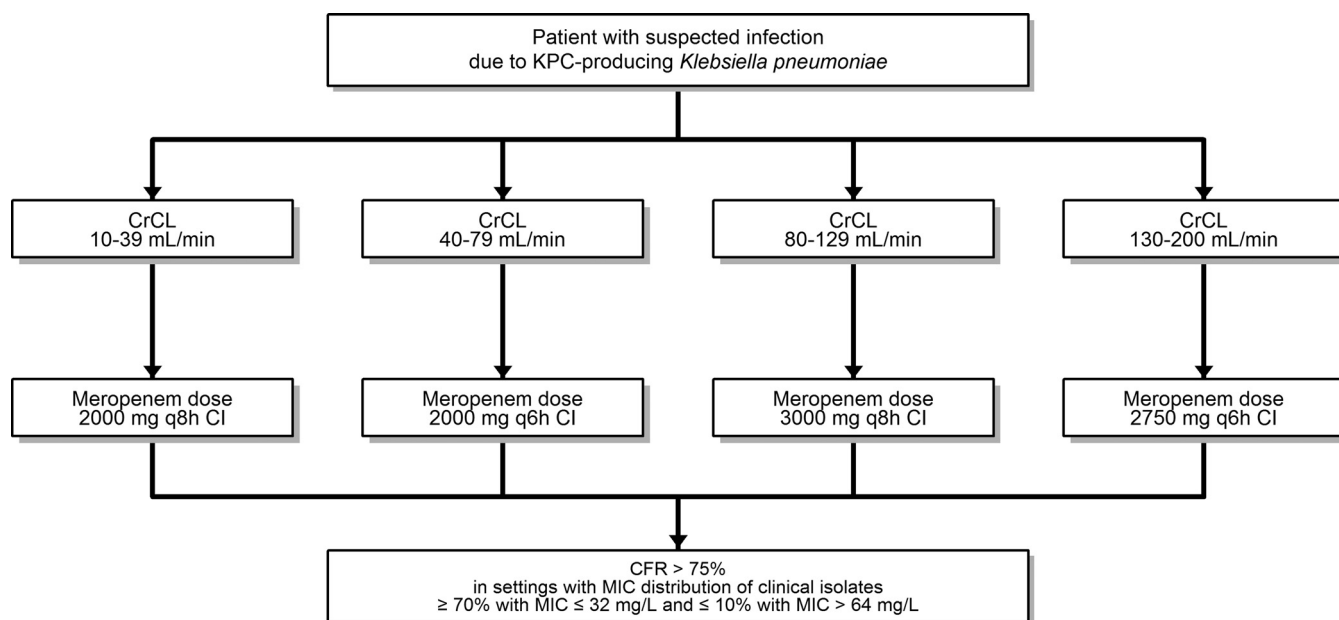


FIG 5 Dosing algorithm for choosing the most advisable high-dose continuous-infusion meropenem regimen in relation to different classes of renal function for the empirical treatment of infection suspected to be caused by *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae* (KPC-Kp). The approach is feasible in clinical settings with frequencies of KPC-Kp of $\geq 70\%$ with meropenem MIC of ≤ 32 mg/liter and with frequencies of KPC-Kp of $\leq 10\%$ with meropenem MIC of > 64 mg/liter. q6h, every 6 h; q8h, every 8 h.

significant predictor of successful clinical and microbiological responses with meropenem in patients with lower respiratory tract infections (27).

A recent meta-analysis of three randomized clinical trials of beta-lactam use showed that the use of CI meropenem in patients with severe sepsis was associated with significantly decreased 30-day in-hospital mortality in comparison with that seen with intermittent infusion (28). These findings should further push clinicians toward a better PK/PD optimization of meropenem use, especially in dealing with KPC-Kp infections.

Our findings suggest that the adoption of permissible HDCl meropenem regimens may be feasible in epidemiological settings with a high frequency of KPC-Kp clinical isolates with a meropenem MIC of ≤ 64 mg/liter. This raises some major issues. In settings of KPC-Kp infection endemicity, knowledge of local prevalence data of KPC-Kp epidemiology is fundamental nowadays. However, the meropenem screening approaches for *in vitro* susceptibility testing of KPC-Kp clinical isolates based on automated systems were often shown to over- and/or underestimate the true MIC value (29, 30). This means that screening approaches in these settings should include broth microdilution methods (29, 30), with a cutoff MIC for meropenem of 64 mg/liter (14). This may allow identifying the proportion of strains with an MIC of ≤ 64 mg/liter for meropenem, whose frequency may vary greatly from hospital to hospital (13, 31, 32). It is worth noting that the frequency was as high as 89.3% among the 169 KPC-Kp clinical isolates included in this study. Interestingly, similar frequencies of meropenem MIC distributions for KPC-Kp clinical isolates were recently reported in the United Kingdom (33, 34). This may helpfully steer clinicians toward including (or not including) permissible HDCl meropenem in combination regimens for the empirical treatment of KPC-Kp infections. It is noteworthy that, in epidemiological settings similar to ours ($\geq 70\%$ of KPC-Kp isolates with a meropenem MIC of ≤ 32 mg/liter and $\leq 10\%$ of KPC-Kp isolates with a meropenem MIC of > 64 mg/liter), the application of our user-friendly HDCl nomogram may predict a CFR of $> 75\%$ in all of the classes of renal function.

We are aware of some potential limits of this study. Some of the dosages in the proposed HDCl meropenem regimens may be higher than the currently licensed dosages. However, this approach was shown to be effective in a retrospective clinical study (14), and it should not be overlooked that there is a great need of improving the clinical outcome of life-threatening infections by MDR Gram-negative bacteria. Additionally, we recognize that the feasibility of our approach is limited to epidemiological settings with a high frequency of infections caused by KPC-Kp isolates with meropenem MICs of up to a maximum of 64 mg/liter and that this may limit the generalizability of the results. Finally, we recognize that the availability of the new beta-lactam/beta-lactamase inhibitor combination ceftazidime/avibactam may represent a potential alternative to this type of strategy.

In conclusion, our PK/PD analysis identified permissible HDCl meropenem regimens that may allow optimal PTAs of 100% $T_{>1-4 \times \text{MIC}}$ for the treatment of infections caused by KPC-Kp with a meropenem MIC up to and including 64 mg/liter. Knowledge of local prevalence data of KPC-Kp based on broth microdilution *in vitro* susceptibility methods with a cutoff value of 64 mg/liter is fundamental for its reliability. In these cases, real-time TDM-guided HDCl meropenem use could be a useful adjunct for optimized care. Although the currently available clinical and experimental data suggest that the toxicity risk of HDCl meropenem regimens should be acceptable, further confirmatory data from prospective studies are warranted.

MATERIALS AND METHODS

Study design. Ninety-seven meropenem steady-state plasma concentrations (C_{ss}) from 30 adult patients with KPC-Kp infections who were enrolled in a previously published retrospective study (14) were used for the development of the population pharmacokinetic model. The patients were treated with antimicrobial combination therapy that included the use of HDCl meropenem optimized by means of real-time therapeutic drug monitoring (TDM). Patient demographic characteristics (age, weight, height, and gender) were retrieved from the original database, together with data pertaining to each TDM instance (meropenem dose and serum creatinine). Creatinine clearance (CrCL) was estimated by means of the Cockcroft-Gault formula (35). The study was approved by the Regional Ethics Committee,

and the requirement for informed written consent was waived due to the retrospective observational design.

Population pharmacokinetic model. Population pharmacokinetic analysis was conducted using the nonparametric adaptive grid (NPAG) approach and the algebraic model solver included in the Pmetrics package (version 1.5.0; Laboratory of Applied Pharmacokinetics and Bioinformatics, Los Angeles, CA, USA) of R (version 3.3.1) (36). Two pharmacokinetic models (a 1-compartment model and a 2-compartment model) with zero-order administration and first-order elimination from the central compartment were developed. Maximum *a posteriori* (MAP) Bayesian estimates of meropenem pharmacokinetic parameters (total clearance [CL], volume of distribution [V], first-order intercompartmental rate constant of transfer from the central compartment to the peripheral compartment and vice versa [k_{cp} and k_{pc} , respectively]) were determined in each patient.

First, a basic model parameterized only for CL and V was developed. Subsequently, the biologically plausible clinical covariates (age, height, weight, gender, CrCL) were tested for potential inclusion in the model by means of the covariate analysis of the Pmetrics function "PMstep." The degree of association between the patient covariates and the median MAP Bayesian estimates of meropenem pharmacokinetic parameters was assessed for each subject by means of linear regression and of forward/backward elimination of covariate.

Comparisons of the performances of the models were evaluated by calculating the objective function value (OFV) and the Akaike information criterion value. A decrease of at least 3.84 points in the OFV was considered statistically significant for addition to the previous model. The goodness of fit and the coefficient of determination of the linear regression of the observed plot versus the predicted plot for both the population predictions and the individual predictions were also taken into consideration. A visual predictive check (VPC) plot was produced to assess the distribution consistency of observed concentrations versus predicted concentrations. Assay error in the population model was estimated by means of the laboratory interday variability assay data. Data were included in a polynomial function to test the correlation existing between drug concentrations and the standard deviation of the observations. Extra process noise was captured with a lambda (L) model ($L = 4.3$).

Monte Carlo simulation for estimation of permissible HDCl meropenem regimens predicting optimal target drug exposure in patients with KPC-Kp infection and with various degrees of renal function. A total of 1,000 subject Monte Carlo simulations for each clinical scenario were conducted using Pmetrics in order to estimate the meropenem C_{ss} values achievable with various candidate HDCl meropenem regimens. Overall, 48 different scenarios were simulated by testing 12 HDCl meropenem regimens (regimen A, 125 mg every 6 h over 6 h; regimen B, 250 mg every 6 h over 6 h; regimen C, 500 mg every 6 h over 6 h; regimen D, 1,000 mg every 8 h over 8 h; regimen E, 1,000 mg every 6 h Cl; regimen F, 1,250 mg every 6 h Cl over 6 h; regimen G, 2,000 mg every 8 h Cl over 8 h; regimen H, 1,750 mg every 6 h over 6 h; regimen I, 2,000 mg every 6 h over 6 h; regimen K, 3,000 mg every 8 h over 8 h; regimen L, 2,500 mg every 6 h over 6 h; regimen M, 2,750 mg every 6 h over 6 h) in relation to four different classes of renal function (10 to 39, 40 to 79, 80 to 129, and 130 to 200 ml/min).

In order to define the permissible HDCl meropenem regimens in the study population, we placed the safety threshold for plasma meropenem C_{ss} at 100 mg/liter. The threshold was arbitrarily assumed in order to prevent any potential theoretical risk of neurotoxicity related to HDCl meropenem. It was adopted in clinical practice in the aforementioned study of TDM-guided optimization of HDCl meropenem in the treatment of patients with KPC-Kp infections (14). The rationale behind this choice was based on the findings of an experimental animal model (37). In that study, it was shown that, after systemic administration of a very high meropenem dose (6.3 mg/min for 45 min) to genetically epilepsy-prone Dilute Brown Agouti DBA/2J (DBA/2) mice, cerebrospinal fluid concentrations of meropenem higher than 100 mg/liter (mean [\pm SD] = 162 mg/liter [\pm 44 mg/liter]) did not induce any seizure. Considering that less than 35% of plasma meropenem concentrations were shown to penetrate into the cerebrospinal fluid in the presence of altered blood-brain barrier (38), we considered this threshold highly safe for avoiding neurotoxicity.

Accordingly, permissible HDCl meropenem regimens were defined as those producing <10 to 15% probabilities of achieving plasma meropenem C_{ss} of >100 mg/liter in each class of renal function.

These dosing regimens were considered sufficiently safe for potential clinical use in this population and were subsequently tested in the pharmacodynamic analysis.

Probability of target attainment (PTA) and cumulative fraction of response (CFR) achievable with the permissible HDCl meropenem regimens. We estimated the PTA with the permissible HDCl regimens of four incremental pharmacodynamic determinants for meropenem efficacy ($100\% T_{>1 \times MIC}$, $100\% T_{>2 \times MIC}$, $100\% T_{>3 \times MIC}$, $100\% T_{>4 \times MIC}$) in relation to the different classes of renal function. These thresholds were defined according to the belief that more-aggressive pharmacodynamic targets might maximize the efficacy of meropenem in critically ill patients with very severe infections (39). Target attainments of >80% in each scenario were acceptable, with a desired level of >90% (40).

The CFRs achievable with the permissible HDCl meropenem regimens were tested against the MIC distribution of the KPC-Kp clinical isolates that were collected routinely at our University Hospital between 2013 and 2016. The microbiological susceptibility of KPC-Kp clinical isolates to meropenem was tested by the broth microdilution method with concentrations ranging between 0.125 and 64 mg/liter and was interpreted according to EUCAST recommendations (susceptible, ≤ 2 mg/liter; resistant, >8 mg/liter).

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